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# Synthesis of crown analogs derived from bisnaphthol

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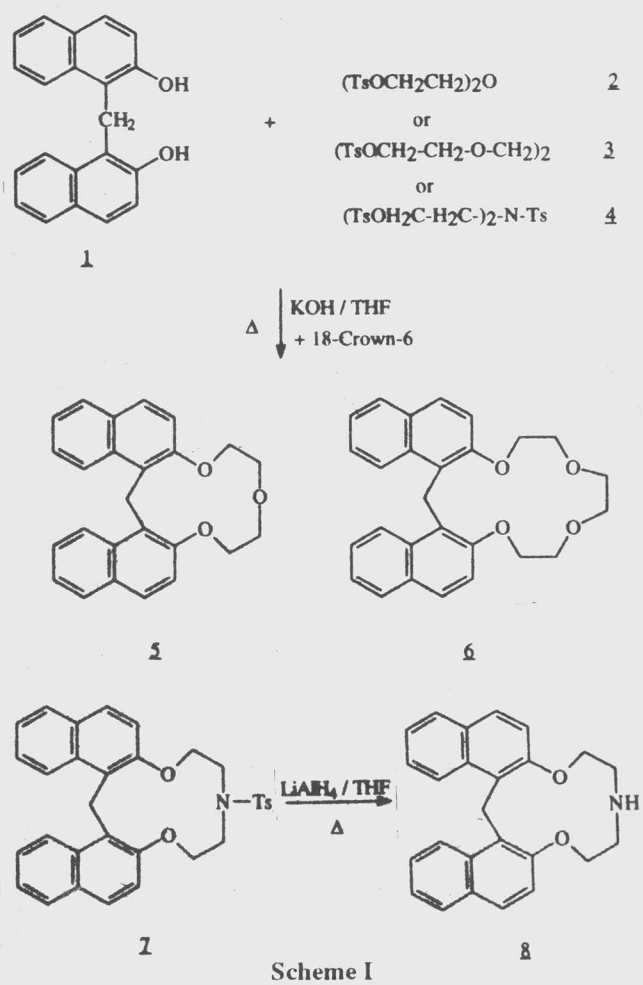
Bisnaphthol **1**, a readily accessible bifunctional phenol, has been cyclocondensed with tosylates **2, 3** and **4** under KOH/THF condition to provide 1:1 dinaphthano crowns **5, 6** and **7**, respectively. The later is detosylated with $LiAlH_4$ to provide **8**. Macrocyclization of **1** with *m*-xylylene dibromide **9** and *p*-xylylene dibromide **10** affords 3:3 condensed macrocycles **11** and **12**, respectively. The structures are supported by elemental analysis, mass and NMR spectral data.

New crown analogs and macrocycles are continually being designed and evaluated for metal ion complexation, host-guest interactions, molecular recognition and other applications[1-3]. Bisnaphthol **1**, a crystalline solid, is readily available by the reaction of β-naphthol with formalin in aqueous sodium acetate[4], and being a bifunctional phenol, it offers the prospects of serving as a useful substrate for elaboration to macrocyclic molecules. Surprisingly, their is only one report concerning the application of this molecule towards the synthesis of a few polyoxa macrocycles[5a].

We have in the present work expanded upon the use of **1** in the area of macrocyclic synthesis and have synthesised besides the known **6**[5a], a number of hitherto unknown macrocycles under more practical and economical conditions.

**Synthesis of dinaphthano-crowns**. First we set up a reaction between **1** and diethylene glycol ditosylate **2** in KOH/THF system containing a catalytic amount of 18-crown-6 as the phase transfer catalyst under high dilution condition. The crude product in $SiO_2$ column chromatography afforded a crystalline solid, m.p. 168-70°C in 31% yield. The compound ($C_{25}H_{22}O_3$) showed $M^+$ at m/z 370 supporting 1:1 macrocyclisation between **1** and **2** (Scheme I). The structure **5**, not reported in the literature, is fully supported by its high resolution NMR spectrum (200 MHz) [δ 3.88 (t, *J*=7 Hz, Ph-O-$CH_2$-$CH_2$-), 4.24 (t, *J*=7 Hz, Ph-O-$CH_2$-$CH_2$), 4.96 (s, Ar-$CH_2$-Ar) and 7.2-8.15 (m, Ar-H)].




Scheme I

The next higher analog **6** has been earlier prepared by Lockhart *et al.*[5a] by the reaction of **1** with triethylene glycol ditosylate **3** using expensive CsF in dry $CH_3CN$ in 22% yield. We

have successfully accomplished this condensation under more economical condition using KOH/THF system and isolated by purification over $SiO_2$ column, the known macrocycle **6**, m.p. 158-60° (lit.[5], m.p. 169°) in comparable yield (21%). The molecule as expected showed $M^+$ at m/z 414 and its spectral data described in the experimental section are in complete agreement with those reported in the literature[5a].

The reaction of **1** with diethanolamine tritosylate **4** was likewise effect under KOH/THF system to afford after $SiO_2$ column chromatography of the crude, a colourless solid, m.p. 224-25° in 18% yield. The 1:1 macrocyclic structure **7** ($M^+$ at m/z 523) was assigned to this compound on the basis of elemental analysis and spectral data.

Although, attempted detosylation of **7** with conc. $H_2So_4$[6] or HBr-phenol[7] proved unsuccessful, the reaction could be successfully realised using $LiAlH_4$ in refluxing THF[8]. The $^1H$ NMR spectrum of the product **8** showed the absence of a signal due to *p*-toluenesulphonyl group and the presence of other relevant signals [δ 3.1 (t, *J*=Hz, >N-C*H*$_2$-CH$_2$), 4.3 (t, *J*=7 Hz, Ar-O-C*H*$_2$-CH$_2$), 2.8 (NH, $D_2O$ exchangeable), 4.9 (s, Ar-C*H*$_2$-Ar)], which fully endorse the structure as **8**. This is the first example of the bisnaphthano macrocycle containing a nitrogen.

The dinaphthano crowns **5, 6, 7** and **8** as pointed out by Lockhart[5] are examples of the two bladed molecular propeller of the type $Ar_2ZX$ (ZX=$CH_2$ in the present cases) which according to Gust and Mislow[9] should have eight stereoisomers. These conformational isomers can have discrete existence only when rotamer interconversions have sufficiently high energy barriers. In agreement with the results of Lockhart[5], we have found that macrocycles **5, 6, 7** and **8** all show sharp $^1H$ NMR signals indicating an apparent equivalence of protons in their NMR spectra[10]. This observation clearly implies that rotamers interconversion are relatively fast on NMR time scale at room temperature resulting in averaged spectra in all cases.

**Macrocyclisation of 1 with *m*- and *p*-xylylene dibromides**. The reaction of **1** with *m*-xylylene dibromide **9** was conducted under the condition employed earlier. Purification of the crude product by $SiO_2$ column chromatography followed by preparative TLC of the enriched major component afforded a colourless crystalline solid, m.p. 278-80° in 16% yield. Its mass spectrum showed $M^+$ at m/z 1206 suggesting the formation of a trimeric macrocycle structure **11**, wherein three molecules each of **1** and **9** are involved in the cyclisation (Scheme II).

The $^1H$ NMR spectrum of **11** exhibited sharp singlets (1:2 ratios) at δ 5.0 and δ 5.2 due to Ar-C*H*$_2$-Ar and Ar-O-C*H*$_2$- protons, respectively. The aromatic protons appeared as a complex multiplet in the range δ 7.0-8.25.

Apart from **11**, products derived either from 1:1 or 2:2 condensation could not be isolated in pure form from the above reaction. Furthermore, inspite of the fact that **11** requires formation of as many as six C-O bonds, the yield of 16% appears reasonably satisfactory from the point of macrocyclisation process[2].

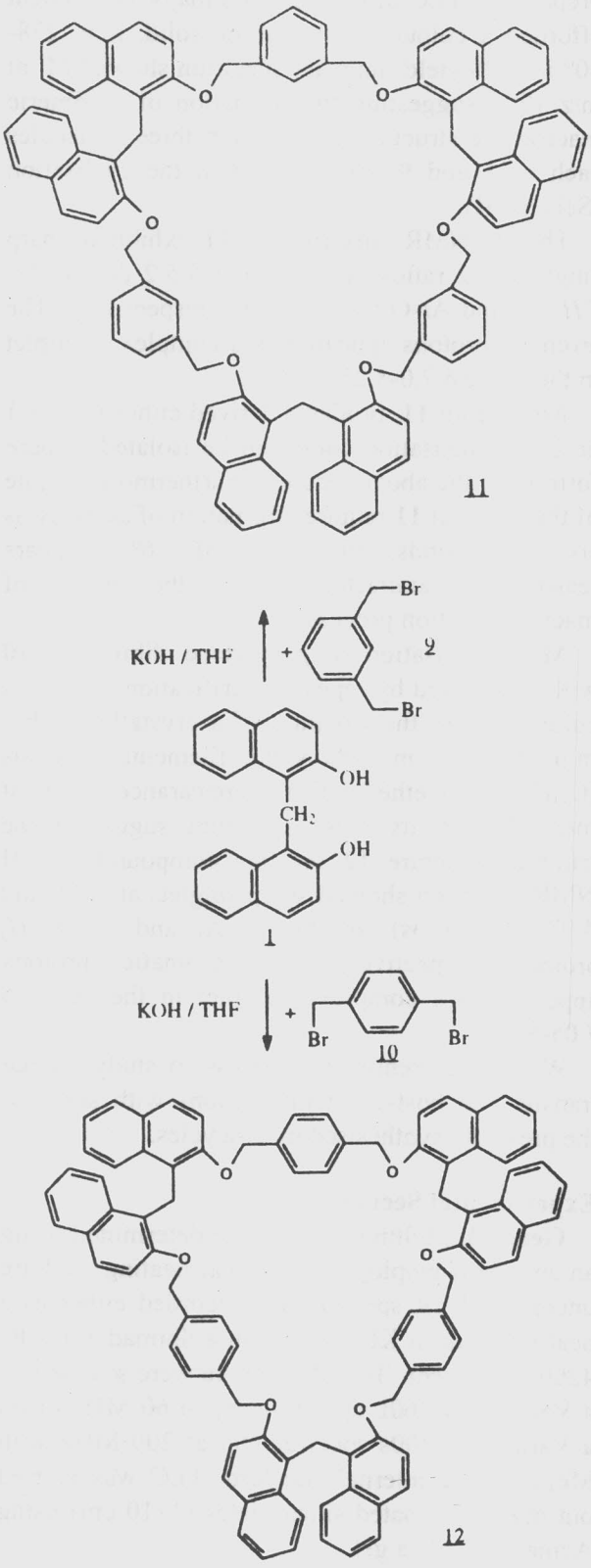
Macrocyclisation of *p*-xylylene dibromide **10** with **1** followed by repeated purification over $SiO_2$ column led to the isolation of a crystalline solid, m.p. 222-26°, in 18% yield. Elemental analysis ($C_{87}H_{66}O_6$) together with the appearance of $M^+$ at m/z 1206 in its mass spectrum suggested the trimeric structure **12** for this compound. Its $^1H$ NMR spectrum showed sharp singlets at δ 4.9 and 4.97 (2:1 ratios) for Ar-C*H*$_2$-Ar and Ar-O-C*H*$_2$ protons, respectively. The aromatic protons appeared as a complex multiplet in the range δ 7.05-8.25.

Work is currently in progress to study charge transfer and host-guest interactions with some of the presently synthesised macrocycles.

## Experimental Section

**General.** Melting points were determined using an apparatus employing electrical heating, and are uncorrected. IR spectra were recorded either as a neat liquid or in KBr pellets on a Shimadzu FTIR-4200 instrument. $^1H$ NMR spectra were scanned on a Varian EM-360L spectrometry at 60 MHz or on a Varian VR-300s spectrometer at 200 MHz with $Me_4Si$ as the internal standard. TLC was carried out manually coated silica plates (3×10 cm) using Acme TLC silica gel.

**General procedure for macrocyclisation of bisnaphthol 1 with tosylates 2, 3 and 4.** Bisnaphthol **1** (3 mmoles) and equimolar amounts




Scheme II

of appropriate tosylate **2** (Ref. 11) or 3 (Ref. 11) or **4** (Ref. 12) were dissolved in THF (100 mL) and added dropwise to a stirred solution of THF (150 mL) containing KOH (0.84 g, 15 mmoles) and 18 crown-6 (50 mg) during 8 hr at 50-56°C. The reaction mixture was further refluxed for 10 hr, cooled to room temperature and filtered through a pad of Celite. The cruse product obtained on solvent removal was chromatographed over $SiO_2$ column using pet. Ether-ethyl acetate (9:1) (for macrocycles **5** and **6**) or pet. Ether-$CH_2Cl_2$ (3:1) (for macrocycles **7**) as eluent to afford the product as a colourless solid. Crystallisation from ethanol-chloroform provided the colourless crystals of macrocycles **5, 6** and **7** in 31%, 21% and 18% yields, respectively.

**Dinaphthano crown 5**. m.p. 168-70° (31% yield); Anal. (Found: C, 81.58; H, 5.46. Calcd for $C_{25}H_{22}O_3$: C, 81.08; H, 5.95%; IR (KBr): 3005, 2950, 1620, 1600, 1510, 1350, 1230, 1150, 1095, 800 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 3.88 (t, 4H, *J*=7 Hz, Ph-O-$CH_2$-C$H_2$-O-), 4.24 (t, 4H, *J*=7 Hz, Ph-O-C$H_2$-$CH_2$-O-), 4.96 (s, 2H, Ar-C$H_2$-Ar) and 7.2-8.15 (m, 12H, Ar-*H*); MS: m/z 370 ($M^+$) (100%), 307, 281, 213 and 169.

**Dinaphthano crown 6**. M.p. 158-60° (lit.[5], m.p. 169°) (21% yield); Anal. (Found: C, 78.66; H, 6.75. $C_{27}H_{26}O_4$: C, 78.26; H, 6.28%; IR (KBr): 3005, 2900, 1620, 1600, 1510, 1460, 1320, 1255, 1280, 1222, 1175, 945, 820 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 3.64 (s, 4H, O-C$H_2$-$CH_2$-O-), 4.25 (t, 4H, Ph-O-C$H_2$-), 3.56 (t, 4H, Ph-O-$CH_2$-C$H_2$-O-), 5.1 (s, 2H, Ph-C$H_2$-Ph), 7.2-7.6 (m, 12H, Ar-H); MS; m/z 414 ($M^+$) (100%), 307, 281, 252, 226.

**Dinaphthano crown 7.** m.p. 224-25° (18% yield); Anal. (Found: C, 73.85; H, 4.82; N, 2.42; S, 6.43. Calcd for $C_{32}H_{27}O_4NS$: C, 73.42; H, 5.16; N, 2.68; S, 6.12%; IR (KBr): 3030, 2900, 1620, 1600, 1512, 1340, 1242, 1150, 1110, 920, 802 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$): 2.3 (s, 3H, C$H_3$-Ar), 4.25 (t, 4H, *J*=7 Hz, Ar-O-C$H_2$), 3.5 (t, 4H, *J*=7 Hz, Ts-N-C$H_2$-$CH_2$), 4.75 (s, 2H, Ar-C$H_2$-Ar) and 7.0-8.0 (m, 16H, Ar-H): MS: m/z 523 ($M^+$) (100%), 415, 390 and 335.

**Preparation of dinaphthano aza crown 8**. Dinaphthano crown **7** (750 mg, 1.435 mmoles) was dissolved in dry THF (40 mL) and the solution stirred at room temperature under $N_2$ atmosphere. To this $LiAlH_4$ (450 mg) was added portionwise

during 15 min. Thereafter, the reaction mixture was refluxed for 10 hr, cooled in ice-bath and excess of $LiAlH_4$ decomposed by cautiously adding 2 mL methanol. The whole mixture was concentrated and the crude product subjected to $SiO_2$ column chromatography using pet. Ether-ethyl acetate (1:1) as eluent to provide a crystalline solid, m.p. 180-82°, in 5% yield (25 mg); Anal. (Found: C, 81.04; H, 6.67; N, 3.25. Calcd. For $C_{25}H_{23}O_2N$: C, 81.30; H, 6.23; N, 3.79%; IR (KBr): 3225, 2950, 1620, 1600, 1520, 1260, 1125, 1020, 780 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$): 3.1 (t, 4H, *J*=7 Hz, >N-C*H*$_2$-$CH_2$), 4.3 (t, 4H, *J*=7 Hz, Ar-O-*CH*$_2$-$CH_2$), 2.8 (s, 1H, >NH, $D_2O$ exchangeable), 4.9 (s, 2H, Ar-C*H*$_2$-Ar) and 7.1-8.0 (m, 12H, Ar-*H*): MS: m/z 369 ($M^+$) (100%), 307 and 142.

**Cyclisation of bisnaphthol 1 with *m*-xylylene dibromide 9**. Using the general procedure, bisnaphthol **1** (1.5 g, 5 mmoles) was reacted with *m*-xylylene dibromide **9** (Ref. 13) (1.315 g, 5 mmoles) in THF.The crude product was subjected to $SiO_2$ column chromatography using pet. Ether-ethyl acetate (4:1) as eluent, and fractions containing the major component were collected. The solid obtained after solvent removal was further purified by preparative TLC using pet. Ether-ethyl acetate (3:1) as irrigant to obtain a white crystalline solid, m.p. 278-80°, in 16.32% yield (328 mg): Anal. Found: C, 86.97; H, 5.12. Calcd for $C_{87}H_{66}O_6$: C, 86.57; H, 5.47; IR (KBr): 3006, 2995, 1622, 1597, 1507, 1300, 1251, 1141, 1087, 930, 800 $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$): 5.0 (s, 6H, Ar-C*H*$_2$-Ar), 5.2 (s, 12H, Ar-O-C*H*$_2$-) and 7.0-8.25 (m, 48, Ar-*H*); MS: m/z 1206 ($M^+$), 907, 804, 613, 460, 414, 408 and 391 9100%).

**Cyclisation of bisnaphthol 1 with *p*-xylylene dibromide 10**. Macrocyclisation of bisnaphthol **1** with *p*-xylylene dibromide **10** (Ref. 13) was carried out on 5 mmole scale under the standard condition. Puyrification of the crude product by $SiO_2$ column chromatography as described above followed by crystallisation from ethanol gave colourless crystals, m.p. 218-20°, in 18% yield (378 mg): Anal. Found: C, 86.08; H, 5.72. Calcd for $C_{87}H_{66}O_6$: C, 86.57; H, 5.47%; IR (KBr): 3006, 2905, 1622, 1598, 1507, 1483, 1260, 1212, 1085, 1010, 800 $cm^{-1}$; $^1H$ NMR (60 MHz, $CdCl_3$): 4.9 (s, 6H, Ar-C*H*$_2$-Ar), 4.97 (s, 12H, Ar-O-C*H*$_2$) and 7.05-8.25 (m, 48H, Ar-*H*); MS: m/z 1206 ($M^+$), 613, 460 (100%), 443 and 341.

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